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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,542	02/15/2002	Guiyi Zhang-Sun	104385-145	8618

7590 05/03/2004

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EXAMINER	
NAFF, DAVID M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 05/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,542	ZHANG-SUN ET AL.	
	Examiner	Art Unit	
	David M. Naff	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/6/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment of 2/17/04 amended claims 1, 2, 4-7, 11, 12, 21 and 24.

Claims examined on the merits are 1-26, which are all claims in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for forming matrix stabilized enzyme crystals when using a polymer as required by claim 11, a multifunctional cross-linking reagent that is a dialdehyde as required by claim 6, an amount of cross-linking reagent as required by claim 8, and forming a cross-linked polymer matrix adhering to the surface of the enzyme crystals, does not reasonably provide enablement for using any polymer, any cross-linking reagent, any amount of cross-linking reagent, and not producing a polymer matrix adhering to the surface of a crystalline enzyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable using any polymer and cross-linking reagent in any amount, and not forming a cross-linked polymer matrix adhering to the surface of enzyme crystals to obtain stabilized

enzyme crystals resistant to degradation by proteolytic enzymes. It would be unpredictable as whether the result of being resistant to protease degradation will be obtained when using conditions substantially different from those used in the specification when obtaining the result of being resistant to protease degradation. The specification discloses that the amount of crosslinking reagent must be low, and clearly higher amounts will not work. The claims must be commensurate in scope with the invention enabled in the specification.

Response to Arguments

Applicants urge that one of skill in the art would be able to use any polymer having reactive moieties capable of interacting with the surface of the crystal enzyme, and also that one would know, from knowledge of the reactive moieties present on the polymer, which cross-linking agents are suitable for use in conjunction with the polymer. This argument is unpersuasive since the invention as described in the specification is not merely a matter of adhering a polymer to an enzyme crystal and cross-linking the polymer, but requires a specific result of making the enzyme crystal resistant to degradation by a protease. It would be unpredictable as to whether this result will be obtained when using a polymer, cross-linking reagent and amount of cross-linking substantially different than disclosed in the specification when obtaining the desired result of being resistant to degradation. Furthermore, claim 23 does not even require cross-linking a polymer and the cross-linked polymer adhering to an enzyme crystal, and there is clearly no enablement in the

specification for obtaining the disclosed result by combining the enzyme crystal with any material that can be considered a matrix and can stabilize the enzyme crystal in any way using any method of combining. Additionally, claims 21-24 do not require producing a matrix adhering to the surface of enzyme crystals, and there is no enablement for obtaining enzyme crystals resistant to a protease without a matrix adhering to the surface of the crystals.

Claim Rejections - 35 USC § 112

Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are confusing and unclear by requiring "matrix stabilized enzyme crystal", and not requiring a matrix to be produced or obtained, and not requiring a physical relationship between the enzyme crystals and the matrix to result in enzyme crystals being stabilized to protease degradation. It is uncertain as to what constitutes the matrix and when the matrix is produced in the process steps carried out in claim 1, and what constitutes the matrix in claims 21-26. In line 5 of claim 1, --- matrix --- should be inserted before "polymer". This insertion should be made in other claims such as 11 that require a "polymer structure". In line 3 of claim 21, after "polylysine" there should be inserted --- to form a cross-linked polylysine matrix structure adhering to the surface of the crystalline phenylalanine ammonia lyase to make the crystalline phenylalanine

ammonia lyase resistant to degradation by proteolytic enzymes ---. Claim 23 should require steps of forming the matrix that stabilizes the enzyme crystals, and require a physical relationship between the matrix and the enzyme crystals that result in making the enzyme crystals resistant to degradation by proteolytic enzymes. In claim 24, line 4, after "agent" there should be inserted --- to form a cross-linked polylysine matrix structure adhering to the surface of the phenylalanine ammonia lyase crystals to make the phenylalanine ammonia lyase crystals resistant to degradation by proteolytic enzymes ---.

Claims 21-26 are confusing and unclear as to the meaning and scope of "stabilized". Being stabilized is relative and subjective. The claims do not specify how the enzyme crystals are stabilized.

In line 5 of claim 1 and where recited in other claims "net-like" is uncertain as to meaning and scope. Being "like" a net is relative and subjective. It is suggested that "net-like" be deleted.

In line 5 of claim 1 and where recited in other claims, "the crystal layer" is confusing by not having clear antecedent basis. It is suggested that "crystal layer" be replaced with --- surface ---. Additionally, to be clear, in line 4, ", effective" should be deleted, and in line 5, "to adhere" should be changed to --- adhering ---.

Dependent claim 11 is confusing by repeating description of the polymer as required by claim 1. The portion of the claim from "having" in line 1 to "a", first occurrence, in 3 should be deleted,

and replaced with --- is selected from the group consisting of ---. With this change, "or" in line 4 should be changed to --- and ---.

For the same type of reason, the portion of claim 12 from "having" in line 1 to "layer" in line 3 should be deleted.

Claims 21 is unclear as to the function of the polylysine and what constitutes the matrix. The claim does not require the polylysine to be cross-linked, and it is not seen how a matrix can result without the polylysine being cross-linked. Additionally, requiring crystalline lyase to be cross-linked in the presence of the polylysine is confusing since it is uncertain as to where the polylysine is present during cross-linking. The specification discloses contacting a polymer with a crystalline enzyme and then cross-linking. This results in cross-linking the polymer, and not the crystalline enzyme.

Claims 23 and 26 are unclear as to what would be the matrix, and the physical relationship between the matrix and the enzyme crystals is uncertain. Are these claims intended to encompass adding any material that can be considered a matrix to enzyme crystals to stabilize the enzyme crystals in any way?

Claims 24 and 25 are unclear as to whether the cross-linked polylysine is the matrix, and the physical relationship between the cross-linked polylysine and the enzyme crystals is uncertain. Are these claims intended to read on producing cross-linked polylysine, and then mixing the cross-linked polylysine with enzyme crystals?

Response to Arguments

While applicants' amendments have overcome some indefiniteness, indefiniteness still remains and in certain instances the amendments have created indefiniteness. The specification cannot be relied on to put clarity in the claims that is not in the claims. The claims and not the specification define metes and bounds of the invention.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4-8, 11-14, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Margolin et al (6,541,606 B2) in view of Mucke (4,940,664) for reasons in the previous office action of 10/14/03 and for reasons herein.

The claims are drawn to a method of forming matrix stabilized enzyme crystals by cross-linking enzyme crystals with a polymer using a multi-functional cross-linking reagent. Also claimed are resultant matrix stabilized enzyme crystals.

Margolin et al discloses stabilizing protein crystals by encapsulating the protein crystals in a polymer (paragraph bridging cols 12 and 13, and paragraph bridging cols 28 and 29) such as poly (amino acids) (col 28, line 52), poly (esters) (col 28, line 53) or polyols (col 28, line 59). The protein crystals may be crosslinked (col 24, line 28 to col 27, line 29) with a multifunctional crosslinking agent containing aldehyde reactive groups (col 25, lines 32-39) such as glutaraldehyde (col 51, line 53). The protein crystal may be an enzyme crystal (col 13, line 20) such as a lyase or lipase (col 16, lines 64 and 66), and the enzyme crystal may crosslinked (col

51, line 50). The amount of crosslinking agent may be 1.5% (col 52, line 46). Rate of dissolution of the polymer encapsulated protein crystals may be modulated by varying polymer crosslinking (col 5, line 47).

Mucke discloses stabilization of carrier-bound enzymes by treatment with a bifunctional crosslinking agent such as glutaraldehyde (col 3, line 22) and a polyamine such as polyethylene imine (col 3, line 30). An enzyme may be bound to an inorganic carrier and the enzyme on the carrier then crosslinked with glutaraldehyde (col 4, lines 30-61) to produce the carrier bound enzyme, which is then treated with glutaraldehyde and polyethylene imine (col 4, lines 64-68).

When producing a polymer encapsulated enzyme crystal as disclosed by Margolin et al, it would have been obvious to use a polyamino acid as the polymer as taught by Margolin et al, and it would have been further obvious to use a glutaraldehyde to crosslink the polyamino acid as suggested by Mucke using glutaraldehyde to crosslink a polyamine on a carrier bound enzyme and by Margolin et al disclosing that rate of dissolution can be modulated by varying polymer crosslinking (col 5, line 47). A polyamino acid polymer disclosed by Margolin et al would have been expected to contain amino groups reactive with aldehyde groups of glutaraldehyde in the same type of way that aldehyde groups of glutaraldehyde react with amino groups of a polyamine when carrying out the process of Mucke. Using polylysine as a polyamino acid as in claim 14 would have been an obvious matter

of choice within the skill of the art. As noted above, Margolin et al disclose using 1.5% crosslinking agent to crosslink enzyme crystals. It would have been obvious to use this amount of crosslinking agent in combination with the polyamino acid polymer, and this amount is less than 2% as required by claim 8.

Response to Arguments

Applicants urge that Margolin et al coat protein crystals with a polymer by coating with a polymer dissolved in an organic solvent and remove the solvent to precipitate the polymer. Applicants point out that in the invention a net-like polymer structure is formed by using the polymer in conjugation with a cross-linking agent. However, the polymer coating of Margolin et al can be considered to be like a net since the polymer can be cross-linked to control dissolution. Margolin et al suggest cross-linking the polymer to control dissolution (col 5, line 47 and col 27, line 43), and it would have been obvious to cross-link a polyamino acid with glutaraldehyde as disclosed by Mucke. A polyamino acid polymer and other polymers disclosed by Margolin et al will have groups that will adhere to the protein crystal. Coating by precipitating the polymer from an organic solvent is not critical to Margolin et al, and it would have been obvious to coat by cross-linking the polyamino acid to insolubilize the polyamino acid as suggested by Mucke.

Claim Rejections - 35 USC § 103

Claims 9, 10, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 1, 2, 4-8,

11-14, 18 and 19 above, and further in view of Margolin et al (6,140,475).

The claims require amounts of crosslinking reagent of 0.5% or less and 0.2% or less.

Margolin et al ('475) disclose crosslinking enzyme crystals to obtain crosslinked enzyme crystals having controlled dissolution by using an amount of glutaraldehyde in a range of about 0.1 to about 0.2% (col 48, line 29).

When modifying Margolin et al ('606) as set forth above by encapsulating enzyme crystals in a polyamino acid polymer crosslinked with glutaraldehyde, it would have been obvious to use an amount of glutaraldehyde as taught by Margolin et al ('475) for obtaining controlled dissolution since Margolin et al ('606) teach that dissolution rate can be modulated by varying polymer crosslinking (col 5, lines 44-47).

Response to Arguments

Applicants rely on arguments above that the invention forms a net-like polymer structure adhering to the enzyme crystals also in regard to this rejection, and the arguments are unpersuasive for reasons set forth above. The coating of Margolin et al can be considered to be net-like since the polymer can be cross-linked, and cross-linking a polyamino acid with glutaraldehdye is suggested by Mucke. It would have been obvious to not precipitate from an organic solvent when using cross-linking to insolubilize the polymer.

Claim Rejections - 35 USC § 103

Claims 3, 15, 20-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims, 2, 4-8, 11-14, 18 and 19 above, and further in view of Eigtved et al (5,753,487).

The claims require the enzyme to be phenylalanine ammonia lyase, and claim 23 requires a method of treating hyperphenylalaninemia with the matrix stabilized enzyme crystals.

Eigtved et al disclose stabilizing phenylalanine ammonia lyase by crosslinking with glutaraldehyde (col 10, lines 25-26), and using the crosslinked phenylalanine ammonia lyase to treat hyperphenylalaninemia (col 12, lines 23-36).

When modifying Margolin et al ('606) as set forth above, it would have been obvious to use phenylalanine ammonia lyase as the enzyme encapsulated to obtain the function of the phenylalanine ammonia lyase to treat hyperphenylalaninemia as suggested by Eigtved et al.

Response to Arguments

Applicants rely on arguments above that the invention forms a net-like polymer structure adhering to the enzyme crystals also in regard to this rejection, and the arguments are unpersuasive for reasons set forth above. The coating of Margolin et al can be considered to be net-like since the polymer can be cross-linked, and cross-linking a polyamino acid with glutaraldehdye is suggested by Mucke. It would have been obvious to not precipitate from an organic solvent when using cross-linking to insolubilize the polymer.

Claim Rejections - 35 USC § 103

Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 3, 15, 20-23 and 26 above, and further in view of Margolin et al ('475).

The claims require an amount of crosslinking agent of less than 0.5% and using polylysine as the polymer when treating hyperphenylalaninemia with phenylalanine ammonia lyase as required by claim 23.

Margolin et al ('475) is described above.

For reasons set forth above when applying Margolin et al ('475), it would have been obvious to use an amount of glutaraldehyde for crosslinking as taught by Margolin et al ('475) for controlled dissolution as the amount of crosslinking agent used to modulate rate of dissolution by varying polymer crosslinking as taught by Margolin et al ('606).

Response to Arguments

Applicants rely on arguments above that the invention forms a net-like polymer structure adhering to the enzyme crystals also in regard to this rejection, and the arguments are unpersuasive for reasons set forth above. The coating of Margolin et al can be considered to be net-like since the polymer can be cross-linked, and cross-linking a polyamino acid with glutaraldehdye is suggested by Mucke. It would have been obvious to not precipitate from an organic solvent when using cross-linking to insolubilize the polymer.

Conclusion

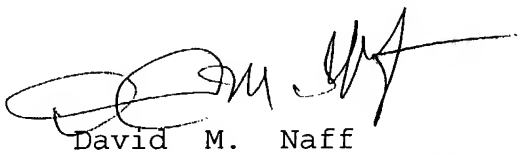
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David M. Naff
Primary Examiner
Art Unit 1651

DMN
5/3/04